THE PATENT OFFICE
STATE HOUSE
66—71 HIGH HOLBORN
LONDON WC1R 4TP

I, the undersigned, being an officer duly authorised in accordance with Section 62(3) of the Patents and Designs Act 1907, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

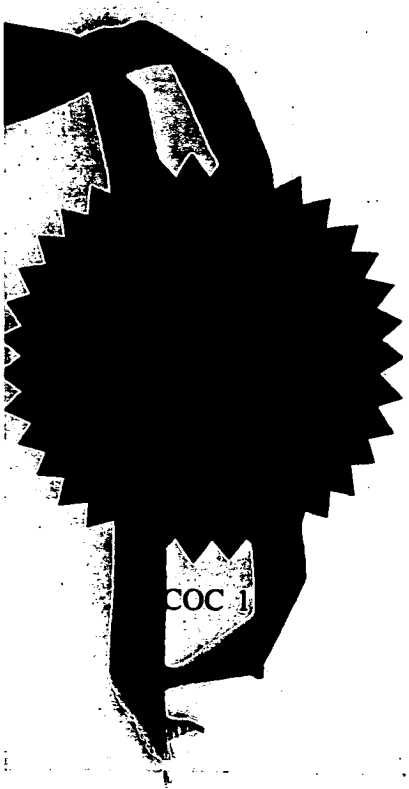
In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words, "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Witness my hand this
15TH day of JULY 1988

W. Russell



PATENTS ACT 1977

PATENTS FORM NO. 1/77 (Revised 1982)

(Rules 16, 19)

The Comptroller
The Patent Office

17 JUN 88

REQUEST FOR GRANT OF A PATENT

8814481.1

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's reference *(Please insert if available)* SG 331

II Title of invention CHEMICAL COMPOUNDS

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) GLAXO GROUP LIMITED,

Country UK State ADP Code No

Address Clarges House, 6/12 Clarges Street, London W1Y 8DH,

Name (of second applicant, if more than one)

Country State

Address

IV Inventor (see note 3)

(a) The applicant is/are the sole/joint inventor(s)

or

(b) A statement on Patents Form No 7/77 is/will be furnished

V Name of Agent (if any) *(See note 4)* ELKINGTON AND FIFE ADP CODE NO

VI Address for Service *(See note 5)*

High Holborn House,
52/54 High Holborn,
London WC1V 6SH.

VII Declaration of Priority *(See note 6)*

Country	Filing date	File number

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) *(See note 7)*

Earlier application or patent number and filing date

IX Check List *(To be filled in by applicant or agent)*

A The application contains the following number of sheet(s)		B The application as filed is accompanied by:-	
1 Request	1 Sheet(s)	1 Priority document	–
2 Description	12 Sheet(s)	Translation of priority document	–
3 Claim(s)	– Sheet(s)	3 Request for Search	–
4 Drawing(s)	– Sheet(s)	4 Statement of Inventorship and Right to Grant	–
5 Abstract	– Sheet(s)		

X It is suggested that Figure No.....of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)*

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.

2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg a "corporation organised and existing under the laws of the State of Delaware, United States of America", trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly (known as) ABC Ltd" are *not* required and should *not* be given. Also enter applicant(s) ADP Code No.(if known).

3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.

4. If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.

5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.

6. The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.

7. When an application is made by virtue of section 8(3), 12(6), 15(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.

8. Attention is directed to rules 90 and 106 of the Patent Rules 1982.

9. Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.

10. Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

CHEMICAL COMPOUNDS

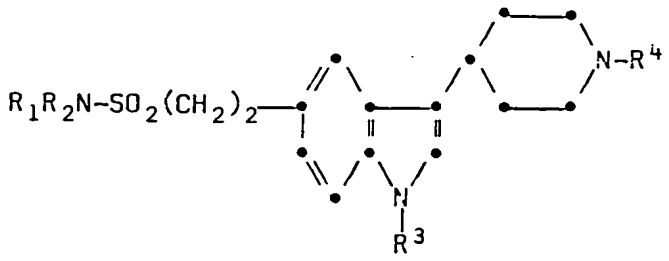
This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

The pain of migraine is associated with excessive dilatation of the cranial vasculature and known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic usually in combination with an antiemetic but such treatments are of limited value.

Recently indole derivatives having selective vasoconstrictor activity have been disclosed in the art as useful in the treatment of migraine [e.g. G.B. 2124210 and 2162522].

We have now found a novel group of indole derivatives which in addition to being potent and selective vasoconstrictors, unexpectedly have a very rapid onset of action following administration, in particular following non-parenteral administration.

Thus the invention provides in a first aspect an indole of the general formula (I).



wherein

R_1 represents a hydrogen atom or a C_{1-6} alkyl group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group;
R_3 represents a hydrogen atom or a C_{1-3} alkyl group;
R_4 represents a hydrogen atom or a C_{1-3} alkyl group
and physiologically acceptable salts and solvates (for example hydrates) therof.

All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof are embraced by the invention.

Referring to the general formula (I), an alkyl group may be a straight chain (such as a methyl or ethyl) or branched chain alkyl group.

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with organic or inorganic acids, for example, hydrochlorides, hydrobromides, sulphates, fumarates and maleates. Other salts may be useful in the preparation of compounds of formula (I), e.g. creatinine sulphate adducts.

A preferred class of compounds represented by the general formula (I) is that wherein R_1 represents a hydrogen atom or a C_{1-3} alkyl group such as a methyl group.

Another preferred class of compounds is that wherein R_2 represents a hydrogen atom or a C_{1-3} alkyl group such as methyl.

Conveniently, R_1 and R_2 when considered together comprise from 1 to 3 carbon atoms.

The substituent R_3 in compounds of general formula (I) may be, for example, a methyl group but is conveniently a hydrogen atom.

The substituent R^4 is conveniently a C_{1-3} alkyl group such as methyl.

Preferred compounds of general formula (I) include :-
N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide and pharmaceutically acceptable salts and solvates thereof.

Compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog, whilst having a negligible effect on blood pressure. Their selective vasoconstrictor action has also been demonstrated <u>in vitro</u>. They are rapidly absorbed from the gastro-intestinal tract and are suitable for oral administration. Following non-parenteral, including intra-duodenal administration, the

compounds of the invention show a very rapid onset of action in animals.

Compounds of the invention are useful in treating pain originating from dilatation of the carotid vascular bed, in particular migraine and cluster headache.

Accordingly, the invention also provides a pharmaceutical composition adapted for use in human medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

In a further aspect there is provided a compound of formula (I) or a salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) in the preparation of a medicament for use in the treatment of pain originating from dilatation of the carotid vascular bed.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man comprising administration of an effective amount of a compound of formula (I) or salt or solvate thereof in particular in the treatment of pain originating from dilatation of the carotid vascular bed.

The compounds according to the invention may for example be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the

art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound

of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, buccal or rectal administration to man (of approximately 70kg bodyweight) for the treatment of migraine is 0.1 to 100mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

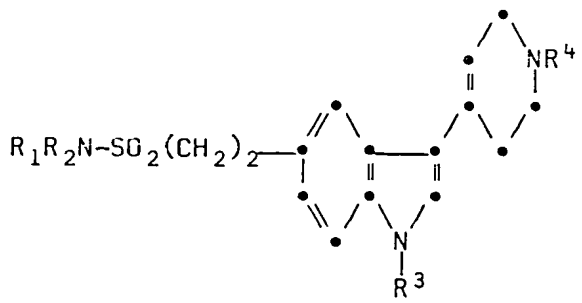
For oral administration a unit dose will preferably contain from 2 to 50 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 5 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 2 mg of a compound of the invention, and capsules and cartridges delivered from an insufflator or an inhaler, contain 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation with an aerosol will be within the range 1 mg to 100 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as for example analgesics, anti-inflammatory agents and anti-nauseants.

Compounds of general formula (I) and physiologically acceptable salts and solvates (e.g. hydrates) thereof, may be prepared by methods known in the art for the preparation of analogous compounds. In particular the compounds of formula (I) maybe prepared by the methods outlined below and which form a further aspect of the invention. In the following processes, R_1, R_2, R_3 and R_4, are as defined for the general formula (I) unless otherwise specified.

According to one general process (A) compounds of formula (I) may be prepared by reduction of the corresponding compounds of formula (II).



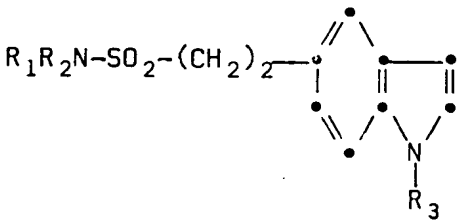
(II)

The compounds of formula (II) are themselves novel compounds and a further part of the invention. The compounds of formula (II) have also been found to be potent and selective vasoconstrictors.

The reduction process may conveniently be carried out in the presence of hydrogen and a noble metal catalyst, such as palladium, Raney nickel, platinum, platinum oxide or rhodium which may be supported, for example, on charcoal. Alternatively a homogenous catalyst such as tris(triphenylphosphine) rhodium chloride may be used. The reduction may be carried out in a solvent such as an alcohol e.g. methanol or ethanol, an ether e.g. dioxan, an ester e.g. ethyl acetate or an amide e.g. dimethylformamide and conveniently at a temperature of from -10 to +50°C.

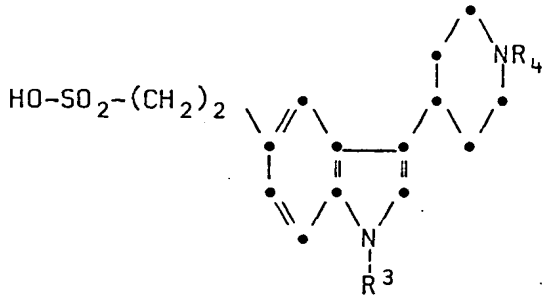
It should be noted however, that the conditions for the reduction of the group -C=CH, to the group -CH-CH_2 may also effect cleavage of any benzyl groups present or reduction of any other alkenyl group present to an alkyl group.

The compounds of formula (II) may be prepared by condensing a compound of formula (III):



(III)

or a protected or activated derivative thereof, with a piperidone of formula (IV):



(V)

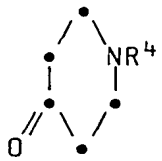
or an acylating agent corresponding thereto, or a salt (for example, an organic or inorganic acid addition salt such as the hydrochloride, hydrobromide, maleate, sulphate or creatinine sulphate adduct) or a protected derivative thereof.

Acylating agents corresponding to the acid of general formula (V) which may conveniently be used in the above process include acid halides, for example sulphonyl chlorides.

The condensation process involving the acylating agents may be effected in a suitable reaction medium and conveniently at a temperature of from -70 to +150°C. Thus the condensation reaction using an acid halide may be effected in a suitable reaction medium such as an amide (e.g. N,N'-dimethylformamide), an ether (e.g. tetrahydrofuran), a nitrile (e.g. acetonitrile), a haloalkane (e.g. dichloromethane) or mixtures thereof, optionally in the presence of a base such as pyridine or triethylamine or an inorganic base as calcium carbonate or sodium bicarbonate.

Where it is desired to prepare a compound of formula (I) in which R_1 and R_2 are both hydrogen atoms, ammonia may be used in the form of aqueous ammonia or in a solvent such as methanol.

Compounds of formula (V) and acylating agents corresponding thereto are novel and as such constitute a further feature of the invention. Compounds of formula (V) or acylating agents corresponding thereto may be prepared by methods analogous to those described in UK Patent Specification 2150932 and 'A Chemistry of Heterocyclic compounds - Indoles Part II', Chapter VI, edited by W. J. Houlihan (1972) Wiley Interscience, New York or by processes, such as process (A), as described herein.



(IV)

or a salt or protected derivative thereof.

The condensation reaction may be effected in a suitable reaction medium in the presence of an acid or a base, conveniently at a temperature of 25 to 120°C.

Acids which may be employed in the above process include organic and inorganic acids such as sulphonic acids (e.g. p-toluenesulphonic acid), carboxylic acids (e.g. acetic acid) and preferably strong inorganic acids such as polyphosphoric acid, sulphuric acid and hydrochloric acid. Suitable solvents for the reaction include inert solvents such as ethers (e.g. tetrahydrofuran or dioxan), alcohols (e.g. ethanol) and chlorinated hydrocarbons (e.g. chloroform or carbon tetrachloride). In some cases the acid may also act as the reaction solvent.

It will be appreciated that in order for the above process to be effected in the presence of a base, R^3 should represent a hydrogen atom.

Bases which may be employed in the above process include alkali metal hydroxides (e.g. potassium hydroxide), alkali metal alkoxides (e.g. sodium or potassium methoxide, ethoxide or t- butoxide), alkali metal hydrides (e.g. sodium hydride) and alkali metal amides (e.g. sodamide). Suitable solvents for the reaction include alcohols (e.g. methanol or ethanol), ethers (e.g. tetrahydrofuran or dioxan) and dimethylsulphoxide.

Intermediates of formula (III) may be prepared by conventional methods for example by reacting an amine of formula R_1R_2NH with the 3-unsubstituted analogues of compounds of formula (V) (as described hereinafter) using the methods described for process (B) hereinafter.

According to another general process (B), a compound of formula (I) may also be prepared by condensing an amine of formula R_1R_2NH with an acid of general formula (V)

According to another general process (C) a compound of formula (I) according to the invention may be converted into another compound of the invention using conventional procedures.

According to one embodiment of this process, a compound of general formula (I) wherein R_4 is a hydrogen atom, may be prepared by reduction of a corresponding compound of general formula (I) wherein R_4 is a benzyl group, for example with hydrogen in the presence of a catalyst e.g. 10% palladium on charcoal.

According to a further embodiment, a compound of general formula (I) where R_2 represents a C_{3-6} alkyl group may be prepared by reduction of the corresponding compound of formula (I) wherein R_2 represents a C_{3-6} alkenyl group. The reduction process may be effected using the conditions as described above for the reduction of the group $CH=CH_2$ in compounds of formula (II).

According to another embodiment of general process (C), a compound of general formula (I) wherein one or more of R_1, R_2, R_3 and R_4 represent hydrogen atoms may be alkylated using conventional techniques. It will be understood that the term 'alkylation' embraces the introduction of an alkyl or alkenyl group. The reaction may be effected using a suitable alkylating agent such as an alkyl halide, alkyl tosylate or dialkylsulphate. The alkylation reaction may conveniently be carried out in an inert organic solvent such as an amide (e.g dimethylformamide) or an ether (e.g. tetrahydrofuran) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides, such as sodium hydride, alkali metal carbonates, such as sodium carbonate or alkali metal alkoxides such as sodium or potassium methoxide, ethoxide or t-butoxide. The alkylation reaction is conveniently carried out at a temperature of from 25 to 100°C.

According to another general process (D), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the preparation of a compound of general formula (I) or a salt thereof it may have been necessary and/or

desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed.J.F.W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene (John Wiley and Sons 1981).

In compounds of general formula (I) wherein R_4 represents hydrogen the group NR_4 may be protected for example by protonation or with a conventional amino protecting group. Such groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl. The indole nitrogen may also be protected, for example by an aralkyl group such as benzyl. Thus, compounds of general formula (I) wherein one or more of the groups R_3 and R_4 represent hydrogen may be prepared by deprotection of a corresponding protected compound.

Removal of any amino protecting groups present may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal); an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation.

As will be appreciated, in some of the general processes (A) to (C) described above it may be necessary or desired to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes (A) to (C).

Thus, according to a further aspect of the invention, the following reactions may, if necessary and/or desired be carried out in any appropriate sequence subsequent to any of the processes (A) to (C).

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate (for example, hydrate) thereof.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I) with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples which should not be construed as constituting a limitation thereto. All temperatures are in ^{0}C.

Intermediate 1

N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-ethane sulphonamide oxalate

A solution of N-methyl-1H-indole-5-ethanesulphonamide (1.0g) in methanol (50mℓ) containing potassium hydroxide (5.6g) and N-methyl-4-piperidone (1.0mℓ) was heated at reflux for 24h, cooled, and the resulting solid filtered off (1.0g). A sample of the solid (0.2g) was dissolved in a hot methanolic solution of oxalic acid (0.06g), the solution cooled, and the salt precipitated by adding ethyl acetate (20mℓ) and dry ether (50mℓ). The salt was filtered off, and dried in vacuo to give the title compound as a solid (0.12g) m.p. 87^{0}-90^{0} (shrinks) Analysis Found: C,52.2;H,5.6;N,9.5.

$C_{17}H_{23}N_3O_2S.C_2H_2O_4.0.6H_2O$ requires C,52.5;H,6.0;N,9.7%.

Example 1

N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethansulphonamide

Intermediate 1 (as the free base) (0.36g, 0.001mol) in absolute alcohol (70mℓ) and anhydrous dimethylformamide (5mℓ) was hydrogenated, in the presence of 5% palladium on activated carbon (0.36g) at ambient temperature and atmospheric pressure. After 20h, hydrogen absorption ($25cm^3$, theoretical = $24cm^3$) ceased. The catalyst was filtered off and the solvent removed in vacuo to give an opaque gum which solidified as a soft white solid (0.3g). Purification by flash chromatography (Sorbsil C60 silica gel, CH_2Cl_2/EtOH/0.88 ammonia; 50:80:1) gave a colourless oil (0.21g) that was triturated with ether to give the title compound (0.17g) m.p. 156-158°. T.l.c. SiO_2 (CH_2Cl_2/EtOH/0.88 ammonia; 50:8:1) Rf 0.4; detection, u.v., IPA.

Water assay	Found :	0.12% w/w ≡ 0.02mol equiv.
Analysis	Found :	C,60.5; H,7.3; N,12.1.
$C_{17}H_{25}N_3O_2S.0.02H_2O$	requires	C,60.8; H,7.5; N,12.5%

(703) 6830500

BACON & THOMAS

Fourth Floor
625 Slaters Lane
Alexandria, Virginia 22314

Oxford et al
filed 8/12/88
DK 5815
Indole Derivatives